Paper No. 26

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DAVID B. WEINER, DAVID N. LEVY, YOSEF REFAELI, WILLIAM WILLIAMS and VELPANDI AYYAVOO

Appeal No. 2001-0759
Application 08/809,186

ON BRIEF

Before Winters, Mills and Grimes, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 14, 15, 17, 21, 24, and 33-36, which are all of the claims pending in this application.

Claim 14 is illustrative of the claims on appeal and reads as follows:

14. A method of inhibiting proliferation of cells which comprise the steps of :
(a) obtaining isolated Vpr protein or a functional fragment thereof; and
(b) contacting cells with an amount of said Vpr protein or a functional fragment thereof effective to inhibit cell proliferation, wherein said cells are T cells and/or B cells and/or monocytes.

The prior art references relied upon by the examiner are:

Levy et al (Levy), "Induction of Cell Differentiation by Human Immunodeficiency Virus 1 vpr," Cell, Vol 72, No. 4, pp. 541-550 (1993)

Bybee et al (Bybee), "Cell Cycle Regulation," Blood Reviews, Vol. 5, No. 3, pp. 177-192 (1991)

Scott et al. (Scott), "Regulation of differentiation, proliferation, and cancer suppressor activity," Internati. J. Develop. Biol., Vol. 37, No. 1, pp. 67-74 (1993)

Wiedermann, et al. (Wiedermann), "Regulation of Myeloid Phagocyte Development and Function by Growth Hormone: A Review," J. Pediatr. Endocrin., Vol. 6, No. 1, pp. 85-91 (1993)

Murphy et al. (Murphy), "Molecular Regulation of Neural Crest Development," Molec. Neurobiol., Vol. 7, No. 2, pp. 111-135 (1993)

Johnson, " Negative Regulators of Cell Proliferation," Pharmacol. Therap., Vol. 62, No. 1-2, pp. 247-265 (1994)

Benet et al. (Benet), "Pharmacokinetics: The Dynamics of Drug Absorption, Distribution and Elimination," Goodman and Gilman's the Pharmacological Basis of Therapeutics, Goodman et al, Eds., Pergamon Press, New York, pp. 3-32 (1990)

Grounds of Rejection

Claims 14, 15, 17, 21, 24, and 33-36 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement as to how to make and use the invention within the scope of the claims. We reverse this rejection.

DISCUSSION

In reaching our decision in this appeal, we have given consideration to the appellants' specification and claims, to the applied prior art references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the noted rejection, we make reference to the examiner's Answer for the examiner's reasoning in support of the rejection, and to the appellants' Brief and Reply Brief for the appellants' arguments thereagainst. As a consequence of our review, we make the determinations which follow.

Background

According to the specification, the invention relates to compounds which modulate glucocorticoid receptor complex transactivation activity. Specification, page 1, lines 4-15. It has been discovered that activation of lymphocytes such as T cells, B-cells and monocytes can be inhibited by vpr, a protein product of HIV-1. Vpr prevents activation of these cells by immunoglobulin molecules. Specification, page 10. Activation of these cells by immunoglobulin molecules results in cytokine production/-

secretion. Accordingly, vpr inhibits cytokine production/secretion by these cells due to immunoglobulin activation. Id. It has been further discovered that vpr acts like steroids in steroid sensitive cells. In addition, vpr is active in steroid non-sensitive cells, i.e., vpr has steroid like activity but is active in a broader spectrum of cells. Specification, pages 10-11.

In particular, the present invention relates to methods of modifying macrophage state of differentiation by contacting macrophage cells with vpr protein. It has been discovered that vpr induces changes in macrophage cells. Specification, page 19. The vpr gene has been shown to increase the kinetics of viral replication and cytopathicity in T-lymphocytes. Specification, page 20. The specification also indicates that an rip-1/vpr complex associates with the activated glucocorticoid receptor (GR) type II receptor complex as part of the signaling pathway for vpr. The rip-1/vpr/GR type II receptor complex translocates into the nucleus in the absence of steroid compounds normally associated with GR-type II receptor translocation. Specification, page 21. It has been discovered that rip-1 is associated with the GR type II receptor complex and that rip-1 co-translocates into the nucleus together with GR-type II receptor when GR-type II receptors are induced to translocate as the result of binding to steroid hormones. As such, according to the specification, these discoveries provide a new target for the modulation of GR-type II complex translocation. The vpr compound and fragments thereof which induce GR -type II complex

translocation are provided which act as non-steroidal therapeutics which mimic steroid activity. Id.

The specification indicates that the functional relationship between vpr function and the glucocorticoid receptor transcriptional pathway is supported by several lines of evidence. Specification, pages 24-26. Glucocorticoids are known to have widespread immunosuppressive effects, and long term exposure of lymphocytes to glucocorticoids induces cell death. Specification, page 25. In example 1 of the specification, when added to a culture of rhabdomyosarcoma cells, vpr protein induced growth arrest and cellular differentiation. Specification, page 45.

35 U.S.C. § 112, first paragraph

Claims 14, 15, 17, 21, 24, and 33-36 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement as to how to make and use the invention within the scope of the claims. The examiner relies on Bybee, Scott, Wiedermann, Murphy, Johnson, Benet and Levy as evidence of lack of enablement.

At the outset, we acknowledge that appellants amended claim 1 in Paper No. 14[1]

[1] Paper No. 14, filed April 30, 1999.

to indicate that the “cells” encompassed by the claims are T cells and/or B cells and/or monocytes. For the reasons herein, it does not appear from the examiner's analysis as set forth in the examiner's answer, that the examiner ever came to grips with, or reconsidered the applicability of the lack of enablement rejection in view of this amendment to claim 1.

Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

In order to establish a prima facie case of lack of enablement, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). See also In re Morehouse, 545 F2d 162, 192 USPQ 29 (CCPA 1976).

Factors to be considered by the examiner in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte

Forman, [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (footnote omitted). In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988). The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement.

The examiner finds the claimed invention is broadly directed towards methods of inhibiting cellular proliferation by contacting cells with Vpr protein, or functional fragments thereof that are sufficient to inhibit cellular proliferation. The claims encompass *in vitro, in vivo, ex vivo* and clinical applications. Answer, page 4. According to the examiner (Id.) the:

> disclosure fails to teach that exogenous Vpr, or functional fragments thereof, are capable of mediating cellular replicative events in cell types of different lineages and states of differentiation. Applicants submit ...that the claimed invention is directed toward a "method of inhibiting cell proliferation which comprises the step of contacting cells with an amount of vpr [sic-Vpr] protein sufficient to inhibit replication." However, the disclosure fails to provide any experimental evidence adducing that Vpr displays the claimed biochemical activities.

In particular, the examiner argues that "[m]any immortalized cell lines routinely used for biochemical investigations already display characteristics of a terminally differentiated phenotype. However other cell lines may retain phenotypic

characteristics of any of the states mentioned *supra* and are likely to be under a complex regulatory cascade dictated by the tissue type." Therefore, the examiner submits "it would appear tenuous to the skilled artisan to conclude that HIV-1 Vpr is capable of modulating differentiation and cellular proliferation in all cell types and lines." Id. The examiner concludes that the specification fails to provide sufficient guidance pertaining to the ability of Vpr to modulate cellular events in vivo or at the clinical level. Answer, pages 5-6. Further, the examiner finds that the specification "fails to provide sufficient guidance pertaining to those cell types (e.g. differentiated; undifferentiated; lymphocytic; tumor cells) that are susceptible to Vpr cellular replicative modulatory functions." Answer, page 5.

It is in this argument that it becomes clear that the examiner believes that the claim scope still encompasses "all cell types and lines" and that the claims are not limited to T cells, B cells and monocytes.

Six of the references in support of the position of lack of enablement of the pending claims are general in nature and are relied for their disclosure that cellular proliferation, differentiation, and development involve a complex series of biochemical and molecular mechanisms that are closely governed by numerous stimulatory and inhibitory factors. Answer, page 5. Only Levy is pertinent to the vpr protein and its activity.

In considering the state of the art, the examiner finds that while Levy teaches vpr-transfected cells (e.g. rhabdomyosarcomas, which are tumors of muscular origin) can be induced to undergo differentiation events, it is not readily manifest that cells contacted with exogenous Vpr will display the same effects. Answer, page 6. According to the examiner the "prior art fails to teach or suggest that exogenously added peptide can induce cellular proliferative events at the extracellular level, or, that Vpr can traverse the cell membrane and enter the cytosolic or nuclear compartments and prevent cellular proliferative activities." Answer, page 7.

The appellants respond to the examiner, arguing the examiner has not established a prima facie case of lack of enablement and has merely made general statements that the art is unpredictable and has concluded that undue experimentation would be required for operability. Brief, page 7. Further, appellants argue that the examiner has not articulated reasons why one of skill in the art, at the time the application was filed, would not have believed that exogenous Vpr protein or fragments thereof, could be delivered to T cells, B cells or monocytes in vivo and result in cell growth arrest. Brief, page 9.

In support of enablement of the pending claims, the appellants argue that even if the examiner had proffered sufficient reasoning to shift the burden of proof to Appellants, the specification discloses the growth inhibitory effect of Vpr protein in both muscle and bone tumor cells *in vitro* and inhibits cell proliferation. Brief, page 12.

In addition, appellants argue that the Declaration under 37 CFR § 1.132 of David B. Weiner and exhibits, submitted on April 27, 1999, provide evidence supporting the operability of the invention. According to appellants, exhibit A presents data showing inhibition of cell proliferation by endogenously expressed Vpr in tumor cells of a variety of types including breast, colon, brain, bladder and fibroblast. Brief, page 13. "Exhibit A also presents data on the ability of endogenously expressed Vpr to suppress the growth of tumor cells in an *in vivo* animal model." Id. "Exhibits B and C together provide evidence pertaining to the ability of exogenously added Vpr to inhibit cellular proliferation in T cells and monocytes *in vitro*." Id. Appellants suggest that those of skill in the art would find such data to be strongly suggestive of the role of Vpr protein in mediating cellular proliferative events in T cells and monocytes, the cell types of the present invention. Id.

In response, the examiner acknowledges that the "Declaration provided by Dr. Weiner reviews the scientific content of these exhibits. The Examiner does not dispute these scientific findings and appropriately drafted claim language directed towards these embodiments would be acceptable." Answer, pages 8-9.

From the examiner's response, it would appear that the examiner has not, in the first instance, properly considered the applicability of the rejection for lack of enablement in view of the pending claim scope, which has already been limited to T cell, B cell and monocyte cell types. Nor has the examiner properly reconsidered the

applicability of the rejection in view of appellants' Declaration evidence. We come to this conclusion upon noting the examiner appears to have accepted the exhibits attached to the Declaration of Dr. Weiner as evidence of the enablement of the claimed invention to inhibiting the proliferation of T-cells and monocytes. We find the examiner proffers no reasoning as to why the evidence presented, supporting the inhibition of proliferation of T-cells and monocytes, would not also support the inhibition of proliferation of B cells.

Upon review of the evidence of lack of enablement provided by the examiner and the argument and evidence of appellants, we find that a preponderance of the evidence supports the position of enablement of claims having the scope of pending claims 14, 15, 17, 21, 24, and 33-36. The rejection of claims 14, 15, 17, 21, 24, and 33-36 for lack of enablement is reversed.

CONCLUSION

The rejection of claims 14, 15, 17, 21, 24, and 33-36. under 35 U.S.C. § 112, first paragraph for lack of enablement to make and use the invention within the scope of the claims is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

)

Sherman D. Winters	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
Demetra J. Mills	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
	)
	)
Eric Grimes	)
Administrative Patent Judge	)

WOODCOCK, WASHBURN, KURTZ
MACKIEWICZ & NORRIS
One Liberty Place, 46th Floor
Philadelphia, PA 19103